Synthesis of Cytosine Radiolysis Products: *cis*- and *trans*-1-Carbamoyl-4,5-dihydroxyimidazolidin-2-one

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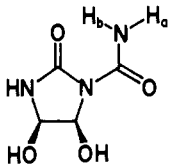
Abstract: The cytosine γ-radiolysis products *cis*- and *trans*-1-carbamoyl-4,5-dihydroxyimidazolidin-2-one (**1**, **2** as racemic modifications) have been synthesized from a common precursor, 1-carbamoyl-4-imidazolin-2-one (**3**). Oxidation of **3** with OsO_4 in aqueous pyridine provided the intermediate *cis*-1-carbamoyl-4,5-dihydroxyimidazolidin-2-one bis(pyridine) cyclic osmate (**8**) which, upon reductive hydrolysis with aqueous $NaHSO_3$, followed by continuous extraction with EtOAc, gave the trans isomer **2**. Treatment of **3** with OsO_4 in dry DMF, followed by reductive cleavage with H_2S, provided the pure cis isomer **1**. The structure of the cis isomer was confirmed by observing (by NMR) its conversion to **8** upon treatment with $Os_2O_6 \cdot py_4$. The assignment of ^1H NMR chemical shifts and coupling constants for the intermediates and products were confirmed in part by examination of additional synthetic models: 2-*N*-methylcarbamoyl-4-imidazolin-2-one, 1-*N*,*N*-dimethylcarbamoyl-4-imidazolin-2-one, and 1-methyl-4-imidazolin-2-one.

The radiation chemistry of nucleic acids has come under increasing scrutiny as chemists seek to ascertain the relationships between ionizing radiation and mutagenesis.[1] Experiments which involve irradiation of aerated aqueous solutions of the individual nucleic acid bases and identification of the radiolysis products can provide important information on the types of base damage one might expect upon in vivo irradiation of polynucleotides, e.g., DNA. With knowledge of both structure and chemical reactivity of the radiolysis products, it is possible to construct sensitive radiochemical assays to quantitate specific types of nucleic acid damage under varying irradiation conditions.[1b,2] Accordingly, once a radiolysis product of a nucleic acid base has been identified, a chemical synthesis is highly desirable to provide the compound in amounts which will allow the determination of chemical and biological properties. Detailed studies of the γ-radiolysis of thymine[3] and thymidine[4] have demonstrated that numerous products are formed, and syntheses of the major products have been reported.[5] More recently, the major products of the γ-radiolysis of cytosine have been isolated and identified.[6] We now report the total synthesis of these products: *cis*- and *trans*-1-carbamoyl-4,5-dihydroxyimidazolidin-2-one (**1**, **2** as racemic modifications).



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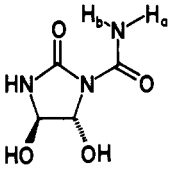

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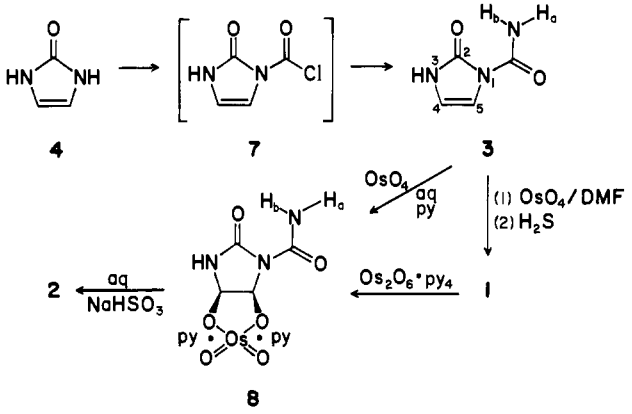
In designing the synthetic approach to these compounds, the paramount concern was the stability of the end product to the final set of reaction conditions, for **1** and **2** were considered susceptible to cis-trans isomerization, dehydration, or oxidation even under mild conditions. For example, the analogous thymine glycols[7,8] and thymidine glycols[9] are reported to undergo cis-trans isomerization. We therefore relied upon controlled oxidation of 1-carbamoyl-4-imidazolin-2-one (**3**) to obtain the "glycol" functionality. To this end, we first prepared 4-imidazolin-2-one (**4**)[10] and investigated procedures for conversion of NH to $NCONH_2$. When a one-step procedure, reaction of **4** with cyanic acid, was unsuccessful we turned to a two-step sequence. The reaction of ethyl chloroformate with **4** under Schotten-Baumann conditions resulted in the formation of a monocarboethoxy derivative, identified as 1-carboethoxy-4-imidazolin-2-one (**5**) by comparison with a sample obtained by the following unambiguous route: reaction of ethoxycarbonyl isocyanate[11] with aminoacetaldehyde diethyl acetal gave *N*-carboethoxy-*N'*-(2,2-diethoxyethyl)urea (**6**) (85%). Treatment of **6** with HCl in aqueous dioxane resulted in hydrolysis of the acetal and ring closure to 1-carboethoxy-4-imidazolin-2-one (**5**). Although the desired 1-carbamoyl-4-imidazolin-2-one (**3**) was not obtained by treatment of **5** with ammonia, which resulted instead in the formation of urethan and 4-imidazolin-2-one, the formation of **5** did demonstrate that acylation of **4** under basic conditions resulted in N- rather than O-acylation. The experiments also indicated the necessity of providing greater differential activation on the external side of the exocyclic carbonyl.

The successful route to 1-carbamoyl-4-imidazolin-2-one (**3**) was initiated by reaction of 4-imidazolin-2-one (**4**) with sodium hydride in anhydrous dioxane (Scheme I). Treatment with

Scheme I



phosgene (1.1 equiv) afforded the carbamoyl chloride intermediate **7** which was not isolated but was treated directly with ammonia to give 1-carbamoyl-4-imidazolin-2-one (**3**) in 45% overall yield following chromatographic purification on silica gel. The novelty of this route lies in its simplicity and in the survival of the compounds en route to the rather rough treatment, i.e., conversion of a substituted urea anion with phosgene followed by ammonia to give a substituted biuret. An NMR assignment that became of later significance in the total project was that of the lower field signal of the two C-H signals for **3** (in $(CD_3)_2SO$), δ 6.78 (dd, 1, J = 1 and 2 Hz, D_2O changes to d, J = 2 Hz) and 6.52 (dd, 1, J = 1 and 2 Hz, D_2O changes to d, J = 2 Hz), to the 5-H on the basis of precedent[12] and the proximity of the 5-H to the nitrogen bearing two carbonyls. The lower field of the two CONH signals, δ 8.14 (br, 1, ex-

changes with D_2O) and 7.64 (br, 1, exchanges with D_2O), was assignable to the hydrogen-bonded proton, i.e., H_b in formula **3**,[13] and the lowest field signal, δ 10.63 (br, 1, exchanges with D_2O), to the ring NH.

Oxidation of compound **3** with 1 equiv of osmium tetroxide in aqueous pyridine resulted in quantitative formation of the bis(pyridine) osmate ester **8**. A significant feature of the NMR spectrum of the cis osmate ester **8** is the spin–spin coupling, J = 6 Hz, between the 4- and 5-H's. Reductive hydrolysis of the osmate ester with aqueous sodium bisulfite, followed by continuous extraction with ethyl acetate, gave a colorless solid (92%) that was shown by NMR to consist of two compounds present in a ratio of 85:15. The major product was isolated by crystallization from methanol–chloroform and was identified as *trans*-1-carbamoyl-4,5-dihydroxyimidazolidin-2-one (**2**), mp 182–183 °C (lit.[6] 173–175 °C); ir (KBr) 1750, 1667 cm^{-1} (lit.[6] 1751, 1667 cm^{-1}). The NMR data for the synthetic material are consistent with the published data if a correction factor of $\Delta\delta$ 0.36–0.40 were to be applied to the values of Hahn et al.,[6] as in the case of the thymine glycols,[9,14] and if their assignments of the 4- and 5-H NMR signals were to be reversed. We assigned the lower field signal of the two C-H signals for **2** (in $(CD_3)_2SO$), δ 5.15 (dd, 1, J = 0.5 and 6 Hz) and 4.55 (dd, 1, J = 1 and 7 Hz), to the 5-H because of its proximity to the nitrogen bearing two carbonyls, as in the case of **3**.

Because cleavage of osmate esters has been demonstrated to occur with 100% Os–O bond cleavage[9] the trans compound **2** must result from isomerization of the initially formed cis glycol **1** from the reductive hydrolysis of compound **8**. In order to isolate the cis glycol **1**, we therefore sought osmate formation and hydrolysis conditions that were not conducive to isomerization. Oxidation of compound **3** with osmium tetroxide in dry dimethylformamide followed by reductive cleavage of the osmate with hydrogen sulfide afforded a colorless solid (61%) that was identical (TLC) with the minor product of the previous sequence. This compound was assigned the structure *cis*-1-carbamoyl-4,5-dihydroxyimidazolidin-2-one (**1**), mp 150–152 °C (lit.[6] 119–122 °C), initially on the basis of its NMR spectrum, which exhibited complex patterns in dimethyl sulfoxide for the 4-H and 5-H due to spin–spin coupling with exchangeable protons and coupled doublets for these two protons upon addition of D_2O. These data are reasonable for the cis glycol **1** although they do not agree with the published data of Hahn et al.,[6] who reported the 4- and 5-H's to be singlets at significantly different chemical shifts from those that we observed.[15]

For final confirmation of the structures assigned to the cis and trans isomers **1** and **2**, we examined their reaction with $Os_2O_6{\cdot}py_4$, since the cis glycol should react to form the osmate ester **8** while the trans glycol should either fail to react or should react at a much slower rate, as in the case of the *cis*- and *trans*-5,6-dihydroxy-5,6-dihydrothymines.[9] Within 1 h of the addition of the osmium reagent to an NMR tube containing the cis glycol **1**, a spectrum identical with that of **8** was obtained. Under the same conditions, addition of $Os_2O_6{\cdot}py_4$ to an NMR tube containing the trans glycol **2** did not produce the spectrum of the cyclic osmate **8** even after 24 h. These experiments confirm the identity of the synthetic glycols and also indicate that trans to cis isomerization does not occur under the stated conditions. With the identity of the synthetic *cis*-1-carbamoyl-4,5-dihydroxyimidazolidin-2-one (**1**) confirmed, we repeated the radiolysis experiments[6] to confirm, if possible, the formation of **1** upon radiolysis of cytosine. We found that from cytosine radiolysis a product was obtained that had chromatographic behavior identical with synthetic **1** and reacted with $Os_2O_6{\cdot}py_4$ to give material chromatographically identical with **8**.

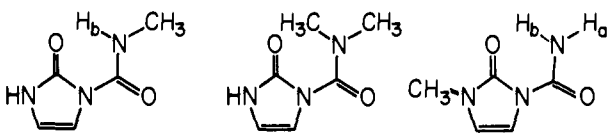
The synthetic route to cytosine radiolysis products **1** and **2** provides a source for investigating further their chemical and biological properties. The observed reaction of the cytosine radiolysis product **1** with $Os_2O_6{\cdot}py_4$ indicates that this reagent would presently not distinguish between radiation-damaged thymine and cytosine residues within a DNA polymer[9] unless chromatographic separation were to be applied at an appropriate level.

Table I. C–H Chemical Shifts for Some Substituted 4-Imidazolin-2-ones[a]

Compound	4-H		5-H	
	δ	$\Delta\delta$	δ	$\Delta\delta$
4-Imidazolin-2-one (**4**)	6.23		6.23	
1-Methyl-4-imidazolin-2-one	6.31	0.08	6.39	0.16
1-Carbamoyl-4-imidazolin-2-one (**3**)	6.52	0.29	6.78	0.55
1-Carbamoyl-3-methyl-4-imidazolin-2-one (**11**)	6.69 (6.68 calcd)		6.87 (6.86 calcd)	

[a] All NMR spectra were recorded in $(CD_3)_2SO$ solution at the same temperature and concentration.

For confirmation of the NMR chemical shift and coupling assignments in the synthetic series (see Experimental Section), the methylated imidazolinones **9**, **10**, and **11** were prepared. Compounds **9** and **10** were readily synthesized by reaction of



9 **10** **11**

methylamine and dimethylamine, respectively, with the carbamoyl chloride **7**. For both compounds, spin–spin coupling was detected in the ^1H NMR spectra between the 4- and 5-H's and an exchangeable proton, the ring NH. Compound **11** was obtained by a synthetic sequence starting with the reaction of methyl isocyanate with α-aminoacetaldehyde diethyl acetal to provide *N*-(2,2-diethoxyethyl)-*N'*-methylurea, which was treated with aqueous acid to afford 1-methyl-4-imidazolin-2-one (**4**, NCH_3). Sequential treatment with sodium hydride, phosgene, and ammonia resulted in the formation of 1-carbamoyl-3-methyl-4-imidazolin-2-one (**11**). The same product was obtained upon treatment of 1-carbamoyl-4-imidazolin-2-one (**3**) with sodium hydride and methyl iodide in anhydrous dimethylformamide. The converging sequences established the identity of the product (**11**). NMR correlations within the series of compounds **4**, **3**, **4** with NCH_3, and **11** revealed that the proton signal undergoing the greater shift upon N-substitution was due to the proton adjacent to that nitrogen and that the effect of each N-substitution was additive for the 4- and 5-H's. Thus, the experimental chemical shifts for the 4- and 5-H's of 1-carbamoyl-3-methyl-4-imidazolin-2-one (**11**) and the empirically calculated values agree within 0.01 ppm (Table I). These NMR correlations will be applied in assigning the structures of other 3-substituted 1-carbamoyl-4-imidazolin-2-ones.

Experimental Section

Melting points were recorded on a Büchi melting point apparatus and are uncorrected. The NMR spectra were recorded on a Varian Associates A-60 or HA-100 spectrometer using tetramethylsilane as an internal standard. In the cases where spin–spin coupling constants are reported to two significant figures, the values were obtained from 50 Hz to fullscale expansions of the relevant sections. The subscripts a and b are used to distinguish between nonequivalent amide protons; H_b refers to the hydrogen-bonded proton. The ultraviolet spectra were

recorded on a Cary Model 15 or a Beckman Acta MVI spectrophotometer. The infrared spectra were obtained on a Perkin-Elmer Model 337 infrared spectrophotometer using KBr pellets unless otherwise noted. Low-resolution mass spectra were recorded on a Varian-MAT CH-5 spectrometer coupled with a 620i computer and STATOS recorder. Microanalyses were performed by Josef Nemeth and his associates, who also weighed samples for the quantitative electronic absorption spectra.

4-Imidazolin-2-one (4) was prepared using a slight modification of the procedure of Duschinsky and Dolan.[10] After stirring a solution of α-ureidoacetaldehyde diethyl acetal (3 g, 17 mmol) in 50 ml of 0.1 N H_2SO_4 at 25 °C for 2 days, it was brought to pH 7 with $Ba(OH)_2$, filtered to remove $BaSO_4$, and concentrated in vacuo to approximately 5 ml. Filtration yielded 1.43 g (80%) of 4-imidazolin-2-one, mp 248–250 °C (lit.[10] 245–248 °C).

***N*-Carboethoxy-*N'*-(2,2-diethoxyethyl)urea (6).** Ethoxycarbonyl isocyanate (4.60 g, 40 mmol)[11] was added dropwise to a solution of α-aminoacetaldehyde diethyl acetal (5.32 g, 40 mmol) in anhydrous ether (100 ml) at 0 °C. The solution was stirred for 1 h, allowed to warm to room temperature, and filtered. Evaporation of the filtrate gave 8.4 g (85%) of a colorless crystalline solid. Recrystallization from low-boiling petroleum ether gave white flakes: mp 72–74 °C; ir 1690, 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (t, 6, J = 7 Hz, acetal CH_3's), 1.30 (t, 3, J = 7 Hz, carboethoxy CH_3), 3.33–3.88 (m, 6, acetal CH_2's and NCH_2), 4.20 (q, 2, J = 7 Hz, carboethoxy CH_2), 4.55 (t, 1, J = 5 Hz, acetal CH), 7.98 (br, 2, 2 NH's); mass spectrum (70 eV) *m/e* (rel intensity), 203 (15, $M^+ - OEt$), 103 (100, $CH(OEt)_2^+$).

Anal. ($C_{10}H_{20}N_2O_5$): C, H, N.

***N*-Carboethoxy-4-imidazolin-2-one (5). Method A.** A solution of *N*-carboethoxy-*N'*-(2,2-diethoxyethyl)urea (2.56 g, 10 mmol) in dioxane (100 ml) was acidified with 20 ml of 1 N HCl. The solution was heated at reflux for 3 h, allowed to cool, and concentrated in vacuo to about 10 ml. After neutralization with 2 N NaOH and evaporation to dryness, the residue was suspended in chloroform and extracted twice with 5 ml of water. The chloroform layer was dried and then evaporated to dryness to give 1.37 g (88%) of a thick oil which crystallized on standing at room temperature. This material was pure enough for further reactions although the NMR spectrum indicated the presence of a small amount of higher molecular weight material. An analytical sample was obtained by sublimation; mp 168 °C; ir 1750, 1800 cm^{-1}; NMR ($CDCl_3$) δ 1.39 (t, 3, J = 7 Hz, CH_3), 4.39 (q, 2, J = 7 Hz, CH_2), 6.31 (m, 1, D_2O addition results in a d, J = 3 Hz, 4-H), 6.66 (m, 1, D_2O addition results in a d, J = 3 Hz, 5-H), 10.25 (br, 1, exchanges with D_2O, NH); mass spectrum (70 eV) *m/e* (rel intensity), 156 (24, M^+), 84 (100, $M^+ - CO_2Et$).

Anal. ($C_6H_8N_2O_3$): C, H, N.

Method B. 4-Imidazolin-2-one (**4**) (420 mg, 5 mmol) was suspended in water (20 ml), sodium hydroxide (200 mg, 5 mmol) was added, and the solution was cooled to 0 °C. Ethyl chloroformate (540 mg, 5 mmol) was added, and the reaction mixture was stirred at 0 °C for 2 h. Extraction with chloroform and evaporation of the chloroform extracts gave compound **5** (369 mg, 47%), identical (TLC and NMR) with the material from Method A.

Attempts to convert the carboethoxy group of **5** into a carbamoyl group by treatment with methanolic ammonia were not successful.

1-Carbamoylimidazolidin-2-one. Imidazolidin-2-one[10] (17.2 g, 0.2 mol) was treated with phosgene (1 equiv) in hot dichloroethane according to the procedure of Ulrich, Tilley, and Sayigh,[16] and the hot mixture was filtered to remove polymeric material and was then allowed to cool to 25 °C. The resulting mixture was treated with a slow stream of ammonia for 2 h, filtered, and the solid was washed with cold water. Recrystallization from ethanol gave 1-carbamoylimidazolidin-2-one (3.5 g, 15%) as colorless flakes: mp 195–198 °C; NMR ($(CD_3)_2SO$) δ 3.2–3.8 (m, 4, CH_2CH_2), 6.90 (br, 1, exchanges with D_2O, NH_a), 7.46 (s, 1, exchanges with D_2O, ring NH), 7.50 (br, 1, exchanges with D_2O, NH_b); mass spectrum (70 eV) *m/e* (rel intensity) 129 (9, M^+), 86 (100, $M^+ - HNCO$).

Anal. ($C_4H_7N_3O_2$): C, H, N.

1-Carbamoyl-4-imidazolin-2-one (3). Sodium hydride (2.30 g of a 50% oil dispersion, 50 mmol) was added to a suspension of 4-imidazolin-2-one (**4**) (4.2 g, 50 mmol) in dry dioxane (300 ml), and the resulting suspension was stirred at 25 °C for 3 h. Phosgene (1.1 equiv as a 10% solution in dioxane) was added, and the reaction mixture was stirred at 25 °C for 2 h. After cooling the mixture to ~15 °C, anhydrous ammonia was slowly bubbled through. After 15 min, the reaction mixture was filtered, and the residue was washed with dioxane. The combined filtrate was evaporated to dryness in vacuo, and the residue was purified by column chromatography (20% EtOH/EtOAc, silica gel) to afford 1-carbamoyl-4-imidazolin-2-one (2.8 g, 45%). The analytical sample was obtained by crystallization from ethanol/ethyl acetate: mp 211–212 °C; $\lambda_{max}^{H_2O}$ ($\epsilon \times 10^{-3}$) at pH 1,236 (4.10); at pH 7, 236 (4.12); at pH 13, 254 (3.05); NMR ($(CD_3)_2SO$) δ 6.52 (dd, 1, J = 1 and 2 Hz, D_2O changes to d, J = 2 Hz, 4-H), 6.78 (dd, 1, J = 1 and 2 Hz, D_2O changes to d, J = 2 Hz, 5-H), 7.64 (br, 1, exchanges with D_2O, $CONH_a$), 8.14 (br, 1, exchanges with D_2O, $CONH_b$), 10.63 (br, 1, exchanges with D_2O, ring NH); mass spectrum (70 eV) *m/e* (rel intensity) 127 (15, M^+), 84 (100, $M^+ - HNCO$).

Anal. ($C_4H_5N_3O_2$): C, H, N.

***cis*-1-Carbamoyl-4,5-dihydroxyimidazolidin-2-one Bis(pyridine) Osmate Ester (8).** Osmium tetroxide (1.0 g, 3.93 mmol) was added to a solution of 1-carbamoyl-4-imidazolin-2-one (**3**) (0.499 g, 3.93 mmol) in 60% aqueous pyridine (25 ml), and the resulting solution was stirred for 6 h at 25 °C. The volatile materials were allowed to evaporate under a gentle stream of nitrogen in an efficient hood. After 10 h, the resulting brown solid was suspended in ether, filtered, and air dried to afford the osmate ester **8** (2.11 g, 100%) in analytical purity. A sample was crystallized from methylene chloride as lustrous black prisms; this compound had no melting point but decomposed slowly upon heating; NMR ($(CD_3)_2SO$) δ 5.45 (dd, 1, J = 1 and 6 Hz, D_2O changes to d, J = 6 Hz, 4-H), 5.93 (dd, 1, J = 0.5 and 6 Hz, D_2O changes to d, J = 6 Hz, 5-H), 6.90 (br, 1, exchanges with D_2O, $CONH_a$), 7.56 (br, 1, exchanges with D_2O, $CONH_b$), 7.60–8,80 (m, 11, part of signal at 8.20 exchanges with D_2O, ring NH and pyridine H's).

Anal. ($C_{14}H_{14}N_5O_6Os$): C, N, Os ($\geq$32.31).

The presence of osmium precludes a hydrogen analysis, and the method used for osmium analysis normally determines 90–95% of the osmium present.

***trans*-1-Carbamoyl-4,5-dihydroxyimidazolidin-2-one (2).** Sodium bisulfite (0.832 g, 8 mmol) was added to a solution of the osmate ester (**8**) (1.079 g, 2.0 mmol) in water (10 ml), and the solution was stirred at 25 °C for 24 h. The mixture that resulted was filtered, and the product was isolated from the filtrate by continuous extraction with ethyl acetate for 24 h, changing the solvent reservoir every 6 h. The combined extracts were evaporated to dryness in vacuo to afford a colorless solid (296 mg, 92%, mp 172–174 °C). This was shown by NMR to be a mixture of cis and trans isomers **1** and **2** in 15:85 proportion. Crystallization from methanol–chloroform gave the pure trans isomer: mp 182–183 °C (lit.[6] 173–175 °C); ir (KBr) 1750, 1667 cm^{-1} (lit.[6] 1751, 1667 cm^{-1}); NMR ($(CD_3)_2SO$) δ 4.55 (dd, 1, J = 1 and 7 Hz, D_2O removes coupling, 4-H), 5.15 (dd, 1, J = 0.5 and 6 Hz, D_2O removes coupling, 5-H), 6.20 (d, 1, J = 7 Hz, exchanges with D_2O, 4-OH), 6.54 (d, 1, J = 6 Hz, exchanges with D_2O, 5-OH), 7.03 (br, 1, exchanges with D_2O, $CONH_a$), 7.51 (br, 1, exchanges with D_2O, $CONH_b$), 8.33 (br, 1, exchanges with D_2O, ring NH).

***cis*-1-Carbamoyl-4,5-dihydroxyimidazolidin-2-one (1).** 1-Carbamoyl-4-imidazolin-2-one (**3**) (254 mg, 2.0 mmol) was dissolved in dimethylformamide (5 ml) and osmium tetroxide (508 mg, 2.0 mmol) was added. The solution was stirred at 25 °C for 16 h and then treated with a slow stream of H_2S for 5 min. The resulting black suspension was allowed to stand at 25 °C for an additional 5 min, filtered, and the residue was washed with additional solvent (5 ml). The combined filtrates were evaporated to dryness in vacuo (<40 °C) to afford an off-white solid. The solid was washed twice with CCl_4 (20 ml), twice with acetone (20 ml), and was air dried to give compound **1** (209 mg, 66%): mp 150–152 °C (lit.[6] 119–122 °C); ir (KBr) 1735, 1667 cm^{-1} (lit.[6] 1739, 1667 cm^{-1}); NMR ($(CD_3)_2SO$) δ 5.03 (ddd, 1, J = 1,6, and 9 Hz, D_2O changes to d, J = 6 Hz, 4-H), 5.38 (dd, 1, J = 6 and 6 Hz, D_2O changes to d, J = 6 Hz, 5-H), 5.58 (d, 1, J = 9 Hz, exchanges with D_2O, 4-OH), 6.40 (d, 1, J = 6 Hz, exchanges with D_2O, 5-OH), 7.00 (br, 1, exchanges with D_2O, $CONH_a$), 7.50 (br, 1, exchanges with D_2O, $CONH_b$), 8.09 (br, 1, exchanges with D_2O, ring NH). Attempted crystallization of this compound from methanol[6] resulted in isomerization to the trans isomer **2**.

Radiolysis of Cytosine. The irradiation of cytosine was carried out under conditions as similar as possible to those of Hahn et al.[6] Cytosine (222 mg, 2.0 mmol) was dissolved in triply distilled water (100 ml). The solution was saturated with oxygen, and a 50-ml portion was transferred to a Pyrex test tube and placed in a ^{137}Cs source (1767 krad/min). The irradiation was continued for 11 h while the solution was saturated with oxygen at 2-h intervals. The solution was then

evaporated to dryness in vacuo (<30 °C), and the residue was extracted with methanol (3×, 5 ml). The methanol extracts were concentrated to ~3 ml and filtered, and the filtrate was examined by TLC. Materials were observed with R_f values equal to the synthetic cis and trans glycols (EtOAc:*i*-PrOH:*n*-PrOH:water 9:1:2:2; cellulose plates; visualized with Ehrlich's reagent). For further confirmation, the methanol solution was evaporated to dryness, the residue was suspended in 1.0 ml methanol, filtered, and a 0.25-ml aliquot was removed. The $Os_2O_6 \cdot py_4$ reagent (~1 mg) was added to this aliquot, and after standing for 5 min at 25 °C, the reaction mixture was examined by TLC (silica gel; 9:1 MeOH:pyridine; 2% thiourea/2 N HCl or uv visualization). Material with an R_f equal to synthetic osmate ester **8** was observed, confirming the presence of the cis glycol in the radiolysis mixture.

1-*N*-Methylcarbamoyl-4-imidazolin-2-one (9). 4-Imidazolin-2-one (**4**) (840 mg, 10 mmol) was treated sequentially with sodium hydride (1.1 equiv) and phosgene (1.1 equiv as a 10% solution in dioxane) in a manner similar to that used in the preparation of compound **3**. The suspension was cooled to 15 °C and treated with a slow stream of methylamine for 15 min. The resulting suspension was allowed to stand at 25 °C for 15 min, filtered, and the residue was washed with dioxane. Evaporation of the combined filtrates and purification of the resulting oil by column chromatography (silica gel, 20% EtOH/EtOAc) gave compound **9** (581 mg, 41%) as a colorless solid. The analytical sample was obtained by sublimation: mp 166–168 °C; NMR ($(CD_3)_2SO$) δ 2.80 (d, 3, J = 5 Hz, D_2O addition changes to s, CH_3), 6.55 (dd, 1, J = 2 and 3 Hz, D_2O changes to d, J = 3 Hz, 4-H), 6.82 (dd, 1, J = 2 and 3 Hz, D_2O changes to d, J = 3 Hz, 5-H), 8.56 (br, 1, exchanges with D_2O, $CONH_b$), 10.67 (br, 1, exchanges with D_2O, ring NH); mass spectrum (70 eV) *m/e* (rel intensity), 141 (13, M^+), 84 (100, $M^+ - MeNCO$).

Anal. ($C_5H_7N_3O_2$): C, H, N.

1-*N,N*-Dimethylcarbamoyl-4-imidazolin-2-one (10). 4-Imidazolin-2-one (**4**) (420 mg, 5 mmol) was treated sequentially with sodium hydride (1.1 equiv) and phosgene (1.1 equiv as a 10% solution in dioxane) in a manner similar to that used in the preparation of compound **3**. The suspension was cooled to 15 °C, treated with a slow stream of dimethylamine for 15 min, and then allowed to stand at 25 °C for 15 min. The resulting suspension was filtered, the residue was washed with dioxane, and the combined filtrates were evaporated to dryness in vacuo. The residue was purified by column chromatography (silica gel, 20% EtOH/EtOAc) to afford compound **10** (294 mg, 38%) in analytical purity: mp 127–129 °C; NMR ($(CD_3)_2SO$) δ 2.94 (s, 6, CH_3's), 6.50 (br s, 2, D_2O changes to AB quartet, J = 3 Hz, 4- and 5-H's), 10.16 (br, 1, exchanges with D_2O, ring NH); mass spectrum (70 eV) *m/e* (rel intensity), 155 (7, M^+), 72 (100, $CON(CH_3)_2^+$).

Anal. ($C_6H_9N_3O_2$): C, H, N.

***N*-(2,2-Diethoxyethyl)-*N'*-methylurea.** Methyl isocyanate (11.4 g, 0.2 mol) in 50 ml of anhydrous benzene was added dropwise to an ice-cold solution of α-aminoacetaldehyde diethyl acetal (26.6 g, 0.2 mol) in benzene (50 ml). After the addition was complete, the solution was heated at reflux for 2 h, allowed to cool, and was then concentrated in vacuo to a thick oil which crystallized on standing to give the substituted urea (38.1 g, 100%) in analytical purity: mp 51–53 °C; NMR ($CDCl_3$) δ 1.22 (t, 6, J = 7, acetal CH_3's), 2.76 (d, 3, J = 5 Hz, NCH_3), 3.36 (q, 2, J = 5, NCH_2), 3.65 (m, 4, acetal CH_2's), 4.51 (t, 1, J = 5 Hz, acetal CH), 5.38 (br, 2, 2 NH's); mass spectrum (70 eV) (rel intensity) 145 (11, $M^+ - OEt$), 103 (100, $CH(OEt)_2^+$).

Anal. ($C_8H_{18}N_2O_3$): C, H, N.

1-Methyl-4-imidazolin-2-one (4, NCH_3). *N*-(2,2-Diethoxyethyl)-*N*-methylurea (3.80 g, 20 mmol) was dissolved in ethanol (200 ml) and 40 ml of 2 N HCl was added. The solution was heated at reflux for 2 h and then allowed to cool to room temperature and neutralized with 2 N NaOH. Extraction with $CHCl_3$ and evaporation of the combined extracts in vacuo gave an off-white solid (1.01 g, 51%). The analytical sample was obtained by sublimation: mp 139–140.5 °C: NMR ($(CD_3)_2SO$) δ 3.08 (s, 3, CH_3), 6.31 (dd, 1, J = 3 and 3 Hz, D_2O changes to d, J = 3 Hz, 4-H), 6.39 (dd, 1, J = 3 and 3 Hz, D_2O changes to d, J = 3 Hz, 5-H), 10.16 br, 1, exchanges with D_2O, NH); mass spectrum (70 eV) *m/e* (rel intensity), 98 (100, M^+).

Anal. ($C_4H_6N_2O$): C, H, N.

1-Carbamoyl-3-methyl-4-imidazolin-2-one (11). Method A. A suspension of 1-methyl-4-imidazolin-2-one (0.85 g, 8.7 mmol) in anhydrous dioxane (50 ml) was treated sequentially with sodium hydride (1.1 equiv), phosgene (1.1 equiv), and anhydrous ammonia as reported for the preparation of compound **3**. The resulting mixture was filtered, the residue was washed with dioxane, and the combined filtrates were concentrated in vacuo to a thick oil. Purification by column chromatography (silica gel, 20% EtOH/EtOAc) gave 1-carbamoyl-3-methyl-4-imidazolin-2-one (**11**) as a colorless solid in analytical purity: mp 159–160 °C; NMR ($(CD_3)_2SO$) δ 3.18 (s, 3, CH_3), 6.69 (d, 1, 4-H), 6.86 (d, 1, 5-H), 7.70 (br, 1, exchanges with D_2O, NH_a), 8.14 (br, 1, exchanges with D_2O, NH_b); mass spectrum (10 eV) *m/e* (rel intensity), 141 (47, M^+), 98 (100, $M^+ - HNCO$).

Anal. ($C_5H_7N_3O_2$); C, H, N.

Method B. 1-Carbamoyl-4-imidazolin-2-one (127 mg, 1 mmol) was dissolved in dimethylformamide (5 ml), and excess methyl iodide was added. Sodium hydride (1 equiv) was added, and the resulting suspension was heated at reflux for 2 h. The solution was then allowed to cool to room temperature and was evaporated to dryness in vacuo. The residue was purified by column chromatography to give **11** (78 mg, 55%) identical (TLC and NMR) with the compound obtained by method A.

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